

Relação entre asma e obesidade na idade pediátrica

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Asthma and obesity during childhood: a review of more than an
occasional association

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Abstract

Introduction: Asthma and obesity are both extremely prevalent diseases in children and their combination represents a different phenotype not explained by the simple addition of both diseases alone.

Objectives: This study was made with the intent of summarizing what has been researched in terms of the connection between asthma and obesity in the past five years.

Methods: For this review, Pubmed was selected as the main source of information. Results were restricted to articles published in the last five years, in English and with full texts available. Out of the two hundred and fifty three articles found, forty five were selected.

Conclusions: It is possible to conclude that it is very likely that there is a connection between asthma and obesity in both directions. It is likely that this phenotype accrues a worse prognosis. Misdiagnosis may be more prevalent in obese children as some symptoms are similar to asthma.

Key Words: Asthma; Obesity; Paediatrics; Obesity Indicators; Asthma Severity

Resumo

Introdução: Quer a asma quer a obesidade são patologias extremamente prevalentes em crianças e a sua conjugação representa um fenótipo diferente, não explicado pela simples adição das duas doenças independentemente.

Objetivos: Este estudo foi feito com o intuito de resumir o que foi investigado em termos de relação entre estas duas patologias nos últimos cinco anos.

Metódos: Neste trabalho, o Pubmed foi utilizado como a principal fonte de informação. Os resultados foram restringidos a artigos publicados nos últimos cinco anos, em Inglês e com textos integrais disponíveis. No final, cerca de quarenta e cinco artigos foram selecionados de entre os duzentos e cinquenta e três inicialmente encontrados.

Conclusão: É possível concluir que uma relação bi-direcional entre a asma e a obesidade é muito provável. É também muito provável que este fenótipo implique um pior prognóstico. É possível que diagnósticos errados sejam prevalentes uma vez que alguns sintomas associados à obesidade são muito similares a sintomas da asma.

Introduction

Asthma, as defined by the Global Initiative for Asthma, is a heterogeneous disease characterized by a chronic inflammation of the airway and by a history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation. [1] It is estimated that as of two thousand and ten, three hundred and thirty-four million people in the World may have asthma. [2] As such, asthma is without a doubt one of the most relevant diseases of the twenty first century.

Obesity is an abnormal or excessive fat accumulation that may impair health as stated in the World Health Organization fact sheet on Obesity and Overweight.[3] Obesity is defined as a weight-for-height greater than three standard deviations above the WHO Child Growth Standards median in children up to five years old and a Body Mass Index greater than two standard deviations above the WHO Growth Reference median in children whose ages range from five to nineteen years old.[3] According to the Global status report on Noncommunicable Diseases 2014, since one thousand nine hundred and eighty the prevalence of obesity has nearly doubled with eleven percent of men and fifteen percent of women aged eighteen years and older being obese in two thousand and four.[4] In the paediatric population an estimated forty two million children (six point three percent) aged under five years were overweight. [4] Developing countries were the ones which had the steepest raise in prevalence.[4]

As such, both diseases can be described as extremely prevalent worldwide and with a significant health impact on both developed and developing countries. The obese asthmatic phenotype also presents different characteristics that cannot be explained by the simple addition of both diseases alone. Therefore, it is important to better understand their relationship that has already been documented several times before. This article was made with the intent of helping to summarize what has been researched in recent years about this topic.

Methods

For this review, Pubmed was selected as the main source of information. The criteria for the selection of an article were the following keywords: asthma, obesity and paediatric. For the purpose of this article, the paediatric population was defined as everyone whose age ranged from zero to nineteen. This range was decided in accordance with the World Health Organization definition. The articles were also filtered by the language, English, available full texts and published in the last five years. The following expression was used to obtain the articles: (((((asthma) AND obesity) AND pediatric) AND "english"[Filter]) AND "loattrfull text"[Filter]) AND "published last 5 years"[Filter]. This search yielded two hundred and fifty three results. Out of the two hundred and fifty-three, seventy-nine were selected. For this first selection, the abstract of every article was read and the main reasons for exclusion were: not mentioning asthma or obesity; mentioning asthma and obesity but not in a context of a possible relationship; not observing the age criteria and being tangential to the topic (for example, only mentioning a link between asthma and obesity in the introduction to another topic).

Out of the seventy-nine, twelve were excluded during the full examination of the articles for not following the specifications mentioned above and nineteen for being review articles whose sources did not fit the determined time period. The only review article used for the writing of this paper was selected on account of having all its references from the year two thousand and fifteen. Forty-eight articles were selected afterwards.

In the end, out of the forty-eight articles, three more were excluded during the second full reading of the articles for not having clinical relevance. The forty-five final articles were then divided in five major topics as seen in the results of the present paper.

Results

Obesity Indicators relation with asthma

According to most of the analysed articles there is a relationship between being obese or overweight and asthma in the paediatric population. Several ways of determining obesity are described in these articles as presenting an association with asthma. The most common parameter related to asthma risk in the obese paediatric population is having a weight over the ninetieth percentile for their age. [5-9] The obesity definition using Body Mass Index-Z by the World Health Organization is also linked to a higher risk of asthma. [10, 11] Benedetti et al. (2015) state that this risk is three times higher than in the non-obese population. [10] Willeboordse et al. (2013), however, state that the positive association between BMI-SDS and asthma is only present in girls, not boys. [12]

Other measurements to define obesity are also related to asthma, as the relationship between a Conicity Index under or equal to one point one and asthma risk in adolescent males – one point eight times higher risk of developing asthma than lean individuals. [10] A Waist-to-Height ratio of over zero point forty-three is concomitant with a higher risk of asthma. [10, 11] According to Benedetti et al. (2015) this risk is one point twenty-four times higher. Benedetti et al (2015) also state that despite a higher prevalence of excess weight (determined by Body Mass Index-Z) and excess abdominal obesity according to Waist-to-Height ratio and Waist Circumference indicators in females and according to Conicity Index in males, the presence of central obesity and high-body weight (at least overweight) as assessed by waist circumference, waist-to-height ratio, and BMI are associated with asthma diagnosis in both genders. [10] Lang et al. (2016) added that waist circumference did not add any information that was not already provided by BMI. [8] Forno et al. (2014) likewise stated that adiposity indicators such as Body Mass Index, percentage of body fat, waist circumference and waist-to-hip ratio are associated with asthma but added that they were also associated with asthma severity/control and atopy. [13] Also according to Forno et al. (2014) atopy significantly mediates the effect of adiposity on asthma. [13]

Another obesity indicator associated with asthma is neck circumference. According to Akin et al. (2016) the presence of a neck circumference greater than the ninetieth percentile is associated with asthma in obese-overweight children. [14] Hacıhamdioglu et al. (2015) add that a neck circumference over the ninetieth percentile is associated with severe asthma in children - severe asthma was defined as children who needed Step three, Step four, or Step five treatment options according to the Global Initiative for Asthma guidelines. [15] Body fat percentage, one more index for obesity, displays a U-shaped association with asthma instead of the linear association between asthma and Body Mass Index therefore implying a greater risk of asthma

for both lower and higher body fat percentages. [16]

Musaad et al (2013) report that children identified as obese/overweight by the Body Mass Index but not by their parents were found to be at a higher risk of asthma when compared to children who were perceived as obese by their parents but not by the Body Mass Index.[17]

Guibas et al. (2013) differentiate the association between obesity indicators and asthma in two age groups: from two to five and from nine to thirteen. In children aged two to five, there was an association between asthma and Conicity Index, waist/hip circumference, Waist-to-Height ratio, skinfold thickness, and skinfold-derived percentage fat mass but not BMI, after adjustments for several confounders.[18] On the other hand, in the group aged nine to thirteen, asthma was positively correlated with Conicity Index, waist circumference, Waist-to-Height ratio, skinfold thickness, skinfold-derived percentage fat mass, Bioelectrical Impedance Analysis derived percentage fat mass and Body Mass Index, after the aforementioned adjustments were made. [18]

Despite most research focusing on the unilateral relationship between obesity and later asthma, past asthma is positively linked with changes in Body Mass Index and the onset of obesity according to Green (2014).[7] However, it is important to note that only new onset asthma is correlated with subsequent changes in BMI.[7] Green (2014) also states that new asthma treatment has a stronger relation with BMI than the new onset of asthma - lagged new asthma treatment is associated with a one point six hundred and forty-one point increase in BMI and a eight point two percent higher risk of being obese while lagged new asthma is associated with a one point two hundred and thirty-five point increase in Body Mass Index and a six point four percent higher risk of being obese.[7] No association between asthma, new asthma, or newly treated asthma and the number of days of aerobic activity or the days of aerobic activity was found. [7] Willeboordse et al. (2016) also did not find any relationship between asthma, Body Mass Index or the association of these two parameters and differences in physical activity. [19] The statements made by Green (2014) are corroborated by Hossain et al. (2015) that describe that children show an increase in the rate of weight gain after the diagnosis of asthma adding that this increase was steeper in females and African-Americans and Hispanics. [20] Ahmadiafshar et al. (2013) also found that asthmatic children were more likely to have a higher BMI than their non-asthmatic counterparts. [21] Furthermore, Ahmadiafshar et al. (2013) state that no relationship between severity, duration of asthma, kind of medication and Body Mass Index was found. [21]

It is important to note that among the forty-five articles reviewed in this study there are also two articles that concluded that no correlation between asthma and Body Mass Index could be found.[22, 23] Another article also mentioned that no relation between weight change in

either direction and the incidence or persistence of asthma could be found. [24] According to Ruotsalainen et al. (2012) weight status has no correlation with asthma or allergy in adolescence after wheezing in infancy. [25]

Topic	Articles in favor	Articles against
Obesity Indicators relation with asthma	12+ 1*+1**	2+1**
Physical activity association with asthma	0	2
Asthma as a risk factor for obesity	3	0

Table 1

*Only in girls

** Depending on the age group

Obesity Indicators relation with asthma	Articles in favor	Articles against
Weight over the ninetieth percentile for their age	5	0
BMI-Z	3+ 1*+1***	2+1**
Conicity Index	2	0
Waist-to-Height ratio	3	0
Waist Circumference	1+ 1***	0
Percentage of Body Fat	2	0
Waist-to-Hip	1+ 1**	0
Neck Circumference	2	0
Skinfold Thickness	1	0
Skinfold-derived percentage fat mass	1	0
Bioelectrical Impedance Analysis derived percentage fat mass	1***	0

Table 2

*Only in girls

** Only in children in the 2-5 age group

*** Only in children in the 9-13 age group

Lung Function

Alterations of lung function also happen in obese, asthmatic and obese asthmatic children. [26] Both a higher Body Mass Index and a high fat mass index are related to a higher respiratory resistance. [26] The distribution of fatty tissue also correlates with lung function alterations such as high android/gynoid fat mass ratio is associated with a lower fraction of exhaled nitric oxide, while a high pre-peritoneal fat mass was associated with a higher fraction of exhaled nitric oxide. [26] The presence and distribution of subcutaneous fat mass was not associated with any respiratory outcome. [26] There is also evidence that inspiratory muscle endurance is reduced in asthmatic obese or overweight adolescents. [27]

Dysanapsis (an incongruence between the growth of the lungs and the airways) has been associated to obesity by Forno et al. (2016). [28] In overweight/obese children with asthma, dysanapsis is associated with higher severity of exacerbations and the use of systemic corticosteroids. [28]

It is interesting to note that spirometric measures of lower airway obstruction decrease with smaller weight increments in obese asthmatic minority children when compared with their white counterparts. [29]

Asthma and Gastro-oesophageal reflux symptoms

As reviewed by Rubin (2015) even though obese patients have a higher risk of developing asthma, they are also more likely to be misdiagnosed. [30] This is mainly due to some asthma symptoms being similar to gastro-oesophageal reflux symptoms in obese children. [30, 31] Obese children have seven times higher odds of reporting gastro-oesophageal reflux symptoms than their lean counterparts. [31] Also important to note that despite gastro-oesophageal reflux symptoms being associated with worse asthma symptoms, it has been reported that these patients have better lung function. [31]

Asthma Control and Severity

Being overweight/obese is a risk factor for having non-controlled asthma. [32] Neck circumference is reported by Maltz et al. (2016) as being associated with asthma control and quality of life in males. [33] Rubin (2015) also reviews that overweight and obese children with early onset asthma tend to have poorer control and a distinct clinical presentation of symptoms with greater dyspnoea and less cough. [30] It is noted as well that these patients have lower exhaled nitric oxide levels and different therapeutic needs with an increased use of short-acting β agonists and less responsiveness to methacholine. [30] Borrell et al. (2013) describe that obesity is associated with a thirty-three percent worse asthma control in boys. [34] The data on girls varied with ethnicity – African-American girls were more likely to have better controlled asthma than their normal weight counterparts, while Mexican-American Girls have a worse asthma control than their lean counterparts. [34] On the other hand, Lu et al. (2016) reported that overweight/obesity was only correlated with asthma prevalence and morbidity in girls and that high fitness was only associated with decreased rates of asthma morbidity in boys but not in girls, independent of weight status. [35]

The association between obesity and a worse asthma control is corroborated by the fact that dietary induced weight loss in overweight and obese asthmatic children leads to significant reduction in severity of exercise-induced bronchoconstriction and improvement of the quality

of life. [36] Moreover, obese asthmatics participating in an active normocaloric diet have reported fewer acute asthma events requiring rescue medication, night time awakenings and could reduce the daily dose of inhaled corticosteroids in eleven out of twenty-six of the patients participating in the diet while obese asthmatics who were on a free diet only managed to reduce the inhaled corticosteroids dosage in six out of twenty-five of the patients in the free diet group. [37]

Obese children with asthma are more likely to go to the emergency department than their overweight and normal weight counterparts. [38] Also noteworthy is the fact that obese paediatric inpatients with acute asthma exacerbations have a significantly higher risk of requiring mechanical ventilation, higher mean total hospital charges, and longer mean length of hospital stay compared to non-obese paediatric inpatients with acute asthma, according to Okubo et al. (2016). [39]

Despite the majority of reviewed articles reporting a link between asthma control/severity and obesity/overweight indicators, there are some opposing results. Lu et al. (2016) report that there was no relation between obesity and worse asthma control or severity in low-income, minority (non-caucasian) children and adolescents with persistent asthma. [40] Yaşar et al. (2015) state that no relationship between BMI and asthma control levels could be found. [41] The results found by Yilmaz et al. (2013) corroborate the absence of a link, adding that no relation could be found even after adjusted for age and gender. [42] Giese (2012) reports that despite obese children having more asthma symptoms, there was not a decline in asthma control. [43] Despite Aragona et al. (2016) finding that overweight/obese pre-school children were two times more likely to have repeated emergency department visits than their lean counterparts, this association was only found within this age group. [9]

Asthma Control and Severity	Articles in favor	Articles against
Obesity/overweight as a risk factor for non-controlled asthma	4+1 *	2+1 **
Neck Circumference as a risk factor for non-controlled asthma	1	0
Gender differences in asthma control	2	0
Weight loss associated with fewer asthmatic symptoms	2	0

Table 1

*Only in pre-school children, no association in other age groups

** Only in low-income, minority (non-caucasian) children and adolescents with persistent asthma

Aetiology and pathophysiology of the obese asthmatic phenotype

According to several reviewed papers there are numerous differences between obese asthmatics and non-obese asthmatics. Kovacic et al. (2015) state that both common and distinct pathogenetic pathways promote asthma in the context of being overweight. [44] Khan et al. (2012) point out that both asthma and obesity are independently and synergistically associated with systemic inflammation - determined by the levels of high-sensitivity C reactive protein. [45] Wahab et al. (2013) found that in obese asthmatics serum leptin was significantly higher and adiponectin was significantly lower when compared with non-obese asthmatic children. [46] Vitamin D deficiency may also participate in the aetiology of the obese asthmatic phenotype as Lautenbacher et al. (2016) state that Vitamin D deficiency is associated with pulmonary function deficits among obese asthmatic children but not among their normal weight counterparts. [47]

Rastogi et al. (2013) found that there is evidence that dysregulated DNA methylation is associated with non-atopic inflammation observed in paediatric obesity-associated asthma. [48]

It is interesting to note that mild obesity induced in asthmatic mice through diet does not augment airway hyperactivity or eosinophilic lung inflammation. [49]

Discussion

By analysing all the data mentioned above it can be concluded that an association between asthma and obesity in the paediatric population is extremely likely. With that being said, the main variable that most articles focused on was whether there was a correlation between asthma and certain obesity indexes and which indexes better associated with the disease. Weight over the ninetieth percentile for their age is the one that had more evidence towards its association with asthma. The Body Mass Index also had the same number of articles in favour of it, which is not surprising as this index is the one used by the World Health Organization in its definition for obesity and it is the most used by physicians since it is the easiest to use. However, this index has also been in the centre of much debate as it is a very simplistic definition of obesity, not accounting for several variables. Since the body mass index only accounts for height and weight, it is very likely that it is not the most useful obesity predictor albeit easy to use. The Body Mass Index was also the only obesity index reviewed in this article that had evidence against its association with asthma.

Other measurements such as the Conicity index, the Waist-to-Height ratio, Waist Circumference, percentage of body fat, Waist-to-Hip ratio, Bioelectrical Impedance Analysis derived percentage fat mass, skinfold thickness, skinfold-derived percentage fat mass and neck circumference have also been associated with asthma. There is not, however, enough evidence to conclude which one is better suited to correlate asthma and obesity. It is also suggested that there may be the need to use different indexes depending on the gender and age of the child but once again there is not enough evidence to state which indexes would be better in each situation. It is suggested that in children aged 2-5, the Conicity Index, waist/hip circumference, Waist-to-Height ratio, skinfold thickness, and skinfold-derived percentage fat mass would be the better measurements while in children aged 9-13 the Conicity Index, Waist Circumference, Waist-to-Height ratio, skinfold thickness, skinfold-derived percentage fat mass, Bioelectrical Impedance Analysis derived percentage fat mass and Body Mass Index would be the better options.

It is interesting to note that the U-shaped association of asthma with body fat percentage suggests that subnutrition, an opposite of obesity, is also associated with a greater risk of asthma. However, this topic is still needing further research since the relationship between asthma and the Body Mass Index is still linear.

If we accept that there is a connection between asthma and obesity, a better correlation between asthma and a certain index may be an indicator that that index is the most reliable measure of obesity, at least in the paediatric population. Nonetheless, it is also important to take

into account that other factors may be involved in this correlation, such as there being a different association between obesity and asthma depending on the pattern of fat distribution.

Important to note is the fact that most reviewed articles focused on the unilateral relationship between obesity and later asthma, i.e, obesity increases the risk for asthma. The few articles that studied the relationship in both directions suggest that asthma is associated with an increase in the Body Mass Index albeit only happening in new onsets of the disease. This increase is believed not to be due to a diminution of physical activity. Asthma increasing the Body Mass Index is further evidence supporting the link between these two diseases as it reinforces the idea of a common pathogenic pathway in both asthma and obesity and that there may be a genetic component.

Even though the aetiology of this relationship is not known yet, the underlying process seems to be a systemic inflammation. Serum leptin is also higher and adiponectin lower in these patients. Vitamin D deficiency also seems to play an important role in obese asthmatic albeit not clear what it does, yet. This underlying processes may be of the utmost importance not only for leading to a better understanding of the obese-asthmatic pattern but also to identify if there are increased risks of other diseases in these patients.

The asthma-obesity phenotype is also associated with a worse asthma control, therefore, weight loss may reduce the severity of the symptoms and the need of rescue medication. These children are also more likely to need to visit the emergency department than their overweight or lean counterparts, which is not surprising considering that their control is worse. In line with this information is the fact that if they require being admitted into hospital, they still have a worse prognosis - higher risk of requiring mechanical ventilation, higher mean total hospital charges, and longer mean length of hospital admission. There is, however, a number of articles stating that either there is no increase in asthma severity/control or that this association is only found in certain groups.

Lung function alterations described above may be partially responsible for this severity increase in the asthmatic-obese phenotype.

Gastro-oesophageal symptoms are of the utmost importance in the discussion of the correlation between asthma and obesity since they are crucial to the discussion of misdiagnosed asthma in obese children. Gastro-oesophageal symptoms may mimic asthma symptoms and, therefore, may induce a wrong diagnosis. This is further supported by the fact that asthmatic-obese children with gastro-oesophageal symptoms have worse asthma symptoms but have better lung function. It is also a possible explanation to why obese asthmatic patients have a worse control of their asthmatic symptoms – it may be a misdiagnosis hence the wrong disease is being treated. This would also be compatible with improvement of the symptoms upon losing

weight.

Conclusion

Asthma and obesity, two extremely prevalent diseases in children worldwide are very likely to be correlated even though the underlying mechanism remains unknown. Further research into the different obesity indexes is warranted since it is not possible yet to determine which one better correlates with the phenotype in question. The Body Mass Index-Z, despite its widespread use, has long been questioned as an obesity index and this research may help in determining better alternatives. It is important to note that weight over the ninetieth percentile for their age and the Body Mass Index-Z are the indexes that have more evidence in favor of a link with asthma amongst the reviewed articles.

Since most research is focused on the risk of asthma in obese children it is also needed to further study the obesity risk in asthmatic children. This knowledge may allow physicians to better understand the aetiology of obesity in the asthmatic-obese children and, therefore, help in determining the most efficient techniques to lose weight in this population. The reviewed data on this topic points towards a two-way relationship between asthma and obesity.

In terms of the aetiology of this process, most of the evidence seems to lead to a systemic inflammation that underlies the obese-asthmatic phenotype. Even though there is evidence pointing to different participating components, a broader understanding and a better integration of the available knowledge is still needed. This better understanding is also crucial for differentiating true cases of obesity and misdiagnosis, which in turn may help clarify whether there is an actual severity increase/worse asthma control in this phenotype or if these results are partly explained by a misdiagnosis.

Evidence also suggests that astmatic-obese children have more symptoms and that those are more difficult to control. On the one hand, what this could mean is that a better understanding of this correlation would even be helpful for healthcare management as these children require more assistance and once admitted to hospital need more thorough care than their overweight or lean counterparts. Even if in the short term costs would go up from financing research, on the long term, a more efficient approach to the disease would help reduce costs that could be used towards other ends. On the other hand, this could be due to a reported misdiagnosis amongst obese-asthmatic children and obese children with gastro-oesophageal reflux symptoms – this could explain the poorer response to medication since a wrong therapy was being employed.

As a conclusion, the relationship between asthma and obesity has been a much researched topic in recent years, yet, there is still much to clarify. This will require a continuous effort from the scientific community to continue progressing so that better treatments and a

better life could be given to all the children presenting this phenotype. The research should be focused both on the aetiology of this bidirectional association as well as on the specific complications and treatments that might arise.

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Attachments

Asthma and Obesity during Childhood: A Review of More than an Occasional Association

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Abstract

Introduction: Asthma and obesity are both extremely prevalent diseases in children and their combination represents a different phenotype not explained by the simple addition of both diseases alone.

Objective: This study was made with the intent of summarizing what has been researched in terms of the connection between asthma and obesity in the past five years.

Methods: For this review, PubMed was selected as the main source of information. Results were restricted to articles published in the last five years, in English and with full texts available. Out of the two hundred and fifty three articles found, forty five were selected.

Conclusion: It is possible to conclude that it is very likely that there is a connection between asthma and obesity in both directions. It is likely that this phenotype accrues a worse prognosis. Misdiagnosis may be more prevalent in obese children as some symptoms are similar to asthma.

Keywords: Asthma; Obesity; Paediatrics; Obesity indicators; Asthma severity

Introduction

Asthma, as defined by the Global Initiative for Asthma, is a heterogeneous disease characterized by a chronic inflammation of the airway and by a history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation [1]. It is estimated that as of two thousand and ten, three hundred and thirty-four million people in the World may have asthma [2]. As such, asthma is without a doubt one of the most relevant diseases of the twenty first century.

Obesity is an abnormal or excessive fat accumulation that may impair health as stated in the World Health Organization fact sheet on Obesity and Overweight [3]. Obesity is defined as a weight-for-height greater than three standard deviations above the WHO Child Growth Standards median in children up to five years old and a Body Mass Index greater than two standard deviations above the WHO Growth Reference median in children whose ages range from five to nineteen years old [3]. According to the Global status report on Noncommunicable Diseases 2014, since one thousand nine hundred and eighty the prevalence of obesity has nearly doubled with eleven per cent of men and fifteen per cent of women aged eighteen years and older being obese in two thousand and four [4]. In the paediatric population an estimated forty two million children (six point three per cent) aged under five years were overweight [4]. Developing countries were the ones which had the steepest raise in prevalence [4].

As such, both diseases can be described as extremely prevalent worldwide and with a significant health impact on both developed and developing countries. The obese asthmatic phenotype also presents different characteristics that cannot be explained by the simple addition of both diseases alone. Therefore, it is important to better understand their relationship that has already been documented several times before. This article was made with the intent of helping to summarize what has been researched in recent years about this topic.

Methods

For this review, PubMed was selected as the main source of information. The criteria for the selection of an article were the following keywords: asthma, obesity and paediatric. For the purpose of this article, the paediatric population was defined as everyone whose age ranged from zero to nineteen. This range was decided in accordance with the World Health Organization definition. The articles were also filtered by the language, English, available full texts and published in the last five years. The following expression was used to obtain the articles: (asthma) AND (obesity) AND (pediatric) AND "English"[Filter]) AND "loattrfull text"[Filter]) and "published last 5 years"[Filter]. This search yielded two hundred and fifty three results. Out of the two hundred and fifty-three, seventy-nine were selected. For this first selection, the abstract of every article was read and the main reasons for exclusion were: not mentioning asthma or obesity; mentioning asthma and obesity but not in a context of a possible relationship; not observing the age criteria and being tangential to the topic (for example, only mentioning a link between asthma and obesity in the introduction to another topic).

Out of the seventy-nine, twelve were excluded during the full examination of the articles for not following the specifications mentioned above and nineteen for being review articles whose sources did not fit the determined time period. The only review article used for the writing of this paper was selected on account of having all its references from the year two thousand and fifteen. Forty-eight articles were selected afterwards.

In the end, out of the forty-eight articles, three more were excluded during the second full reading of the articles for not having clinical relevance. The forty-five final articles were then divided in five major topics as seen in the results of the present paper.

Results

Obesity indicators relation with asthma

According to most of the analysed articles there is a relationship between being obese or overweight and asthma in the paediatric population. Several ways of determining obesity are described in these articles as presenting an association with asthma. The most common parameter related to asthma risk in the obese paediatric population is having a weight over the ninetieth percentile for their age [5-9]. The obesity definition using Body Mass Index-Z by the World Health Organization is also linked to a higher risk of asthma [10,11]. Benedetti et al. state that this risk is three times higher than in the non-obese population. [10] Willeboordse et al. however, state that the positive association between BMI-SDS and asthma is only present in girls, not boys [12].

Other measurements to define obesity are also related to asthma, as the relationship between a Conicity Index under or equal to one point one and asthma risk in adolescent males – one point eight times higher risk of developing asthma than lean individuals [10]. A Waist-to-Height ratio of over zero point forty-three is concomitant with a higher risk of asthma [10,11]. According to Benedetti et al. this risk is one point twenty-four times higher. Benedetti et al. also state that despite a higher prevalence of excess weight (determined by Body Mass Index-Z) and excess abdominal obesity according to Waist-to-Height ratio and Waist Circumference indicators in females and according to Conicity Index in males, the presence of central obesity and high-body weight (at least overweight) as assessed by waist circumference, waist-to-height ratio and BMI are associated with asthma diagnosis in both genders [10]. Lang et al. added that waist circumference did not add any information that was not already provided by BMI [8]. Forno et al. likewise stated that adiposity indicators such as Body Mass Index, percentage of body fat, waist circumference and waist-to-hip ratio are associated with asthma but added that they were also associated with asthma severity/control and atopy [13]. Also according to Forno et al. atopy significantly mediates the effect of adiposity on asthma [13].

Another obesity indicator associated with asthma is neck circumference. According to Akin et al. the presence of a neck circumference greater than the ninetieth percentile is associated with asthma in obese-overweight children [14]. Hacıhamdioglu et al. add that a neck circumference over the ninetieth percentile is associated with severe asthma in children - severe asthma was defined as children who needed Step three, Step four, or Step five treatment options

according to the Global Initiative for Asthma guidelines [15]. Body fat percentage, one more index for obesity, displays a U-shaped association with asthma instead of the linear association between asthma and Body Mass Index therefore implying a greater risk of asthma for both lower and higher body fat percentages [16].

Musaad et al. report that children identified as obese/overweight by the Body Mass Index but not by their parents were found to be at a higher risk of asthma when compared to children who were perceived as obese by their parents but not by the Body Mass Index [17].

Guibas et al. differentiate the association between obesity indicators and asthma in two age groups: from two to five and from nine to thirteen. In children aged two to five, there was an association between asthma and Conicity Index, waist/hip circumference, Waist-to-Height ratio, skinfold thickness and skinfold-derived percentage fat mass but not BMI, after adjustments for several confounders [18]. On the other hand, in the group aged nine to thirteen, asthma was positively correlated with Conicity Index, waist circumference, Waist-to-Height ratio, skinfold thickness, skinfold-derived percentage fat mass, Bioelectrical Impedance Analysis derived percentage fat mass and Body Mass Index, after the aforementioned adjustments were made [18].

Despite most research focusing on the unilateral relationship between obesity and later asthma, past asthma is positively linked with changes in Body Mass Index and the onset of obesity according to Green [7]. However, it is important to note that only new onset asthma is correlated with subsequent changes in BMI [7]. Green also states that new asthma treatment has a stronger relation with BMI than the new onset of asthma - lagged new asthma treatment is associated with a one point six hundred and forty-one point increase in BMI and a eight point two per cent higher risk of being obese while lagged new asthma is associated with a one point two hundred and thirty-five point increase in Body Mass Index and a six point four per cent higher risk of being obese [7]. No association between asthma, new asthma, or newly treated asthma and the number of days of aerobic activity or the days of aerobic activity was found [7]. Willeboordse et al. also did not find any relationship between asthma, Body Mass Index or the association of these two parameters and differences in physical activity [19]. The statements made by Green [7] are corroborated by Hossain et al. that describe that children show an increase in the rate of weight gain after the diagnosis of asthma adding that this increase was steeper in females and African-Americans and Hispanics [20]. Ahmadiashar et al. also found that asthmatic children were more likely to have a higher BMI than their non-asthmatic counterparts [21]. Furthermore, Ahmadiashar et al. state that no relationship between severity, duration of asthma, kind of medication and Body Mass Index was found [21].

It is important to note that among the forty-five articles reviewed in this study there are also two articles that concluded that no correlation between asthma and Body Mass Index could be found [22,23]. Another article also mentioned that no relation between weight change in either direction and the incidence or persistence of asthma could be found [24]. According to Ruotsalainen et al. weight status has no correlation with asthma or allergy in adolescence after wheezing in infancy [25] (Tables 1 and 2).

Topic	Articles in favor	Articles not in favor
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Obesity Indicators relation with asthma	12+1*+1**	2+1**
Physical activity association with asthma	0	2
Asthma as a risk factor for obesity	3	0

Table 1: Association of asthma with obesity indicators, physical activity and risk factor for obesity (*Only in girls; **Depending on the age group).

Obesity Indicators relation with asthma	Articles in favor	Articles not in favor
Weight over the ninetieth percentile for their age	5	0
BMI-Z	3+1*+1***	2+1**
Conicity Index	2	0
Waist-to-Height ratio	3	0
Waist Circumference	1+1***	0
Percentage of Body Fat	2	0
Waist-to-Hip	1+1**	0
Neck Circumference	2	0
Skinfold Thickness	1	0
Skinfold-derived percentage fat mass	1	0
Bioelectrical Impedance Analysis derived percentage fat mass	1***	0

Table 2: Obesity indicators relation with asthma (*only girls, **only children in 2-5 age group, ***only children in 9-13 age group).

Lung function

Alterations of lung function also happen in obese, asthmatic and obese asthmatic children [26]. Both a higher Body Mass Index and a high fat mass index are related to a higher respiratory resistance [26]. The distribution of fatty tissue also correlates with lung function alterations such as high android/gynoid fat mass ratio is associated with a lower fraction of exhaled nitric oxide, while a high pre-peritoneal fat mass was associated with a higher fraction of exhaled nitric oxide [26]. The presence and distribution of subcutaneous fat mass was not associated with any respiratory outcome [26]. There is also evidence that inspiratory muscle endurance is reduced in asthmatic obese or overweight adolescents [27].

Dysanapsis (an incongruence between the growth of the lungs and the airways) has been associated to obesity by Forno et al. [28]. In overweight/obese children with asthma, dysanapsis is associated with higher severity of exacerbations and the use of systemic corticosteroids [28].

It is interesting to note that spirometric measures of lower airway obstruction decrease with smaller weight increments in obese asthmatic minority children when compared with their white counterparts [29].

Asthma and gastro-oesophageal reflux symptoms

As reviewed by Rubin even though obese patients have a higher risk of developing asthma, they are also more likely to be misdiagnosed [30]. This is mainly due to some asthma symptoms being similar to gastro-oesophageal reflux symptoms in obese children [30,31]. Obese

children have seven times higher odds of reporting gastro-oesophageal reflux symptoms than their lean counterparts [31]. Also important to note that despite gastro-oesophageal reflux symptoms being associated with worse asthma symptoms, it has been reported that these patients have better lung function [31].

Asthma control and severity

Being overweight/obese is a risk factor for having non-controlled asthma [32]. Neck circumference is reported by Maltz et al. as being associated with asthma control and quality of life in males [33]. Rubin also reviews that overweight and obese children with early onset asthma tend to have poorer control and a distinct clinical presentation of symptoms with greater dyspnoea and less cough [30]. It is noted as well that these patients have lower exhaled nitric oxide levels and different therapeutic needs with an increased use of short-acting β agonists and less responsiveness to methacholine [30]. Borrell et al. describe that obesity is associated with a thirty-three percent worse asthma control in boys [34]. The data on girls varied with ethnicity-African-American girls were more likely to have better controlled asthma than their normal weight counterparts, while Mexican-American Girls have a worse asthma control than their lean counterparts [34]. On the other hand, Lu et al. reported that overweight/obesity was only correlated with asthma prevalence and morbidity in girls and that high fitness was only associated with decreased rates of asthma morbidity in boys but not in girls, independent of weight status [35].

The association between obesity and a worse asthma control is corroborated by the fact that dietary induced weight loss in overweight

and obese asthmatic children leads to significant reduction in severity of exercise-induced bronchoconstriction and improvement of the quality of life [36]. Moreover, obese asthmatics participating in an active normocaloric diet have reported fewer acute asthma events requiring rescue medication, night time awakenings and could reduce the daily dose of inhaled corticosteroids in eleven out of twenty-six of the patients participating in the diet while obese asthmatics who were on a free diet only managed to reduce the inhaled corticosteroids dosage in six out of twenty-five of the patients in the free diet group [37].

Obese children with asthma are more likely to go to the emergency department than their overweight and normal weight counterparts [38]. Also noteworthy is the fact that obese paediatric in patients with acute asthma exacerbations have a significantly higher risk of requiring mechanical ventilation, higher mean total hospital charges, and longer mean length of hospital stay compared to non-obese paediatric in patients with acute asthma, according to Okubo et al. [39].

Asthma Control and Severity	Articles in favor	Articles not in favor
Obesity/overweight as a risk factor for non-controlled asthma	4+1*	2+1**
Neck Circumference as a risk factor for non-controlled asthma	1	0
Gender differences in asthma control	2	0
Weight loss associated with less asthmatic symptoms	2	0

Table 3: Asthma control and severity (*only in pre-school children, no association in other age groups; **only in low-income, minority (non-Caucasian) children and adolescents with persistent asthma).

Aetiology and physiopathology of the obese asthmatic phenotype

According to several reviewed papers there are numerous differences between obese asthmatics and non-obese asthmatics. Kovacic et al. state that both common and distinct pathogenetic pathways promote asthma in the context of being overweight [44]. Khan et al. point out that both asthma and obesity are independently and synergistically associated with systemic inflammation - determined by the levels of high-sensitivity C reactive protein. [45]. Wahab et al. found that in obese asthmatics serum leptin was significantly higher and adiponectin was significantly lower when compared with non-obese asthmatic children [46]. Vitamin D deficiency may also participate in the aetiology of the obese asthmatic phenotype as Lautenbacher et al. states that Vitamin D deficiency is associated with pulmonary function deficits among obese asthmatic children but not among their normal weight counterparts [47].

Rastogi et al. found that there is evidence that dysregulated DNA methylation is associated with non-atopic inflammation observed in paediatric obesity-associated asthma [48].

It is interesting to note that mild obesity induced in asthmatic mice through diet does not augment airway hyperactivity or eosinophilic lung inflammation [49].

Discussion

By analysing all the data mentioned above it can be concluded that an association between asthma and obesity in the paediatric population is extremely likely. With that being said, the main variable that most articles focused on was whether there was a correlation

Despite the majority of reviewed articles reporting a link between asthma control/severity and obesity/overweight indicators, there are some opposing results. Lu et al. report that there was no relation between obesity and worse asthma control or severity in low-income, minority (non-Caucasian) children and adolescents with persistent asthma [40]. Yaşar et al. state that no relationship between BMI and asthma control levels could be found [41]. The results found by Yilmaz et al. corroborate the absence of a link, adding that no relation could be found even after adjusted for age and gender [42]. Giese reports that despite obese children having more asthma symptoms, there was not a decline in asthma control [43]. Despite Aragona et al. finding that overweight/obese pre-school children were two times more likely to have repeated emergency department visits than their lean counterparts, this association was only found within this age group [9] (Table 3).

between asthma and certain obesity indexes and which indexes better associated with the disease. Weight over the ninetieth percentile for their age is the one that had more evidence towards its association with asthma. The Body Mass Index also had the same number of articles in favour of it, which is not surprising as this index is the one used by the World Health Organization in its definition for obesity and it is the most used by physicians since it is the easiest to use. However, this index has also been in the centre of much debate as it is a very simplistic definition of obesity, not accounting for several variables. Since the body mass index only accounts for height and weight, it is very likely that it is not the most useful obesity predictor albeit easy to use. The Body Mass Index was also the only obesity index reviewed in this article that had evidence against its association with asthma.

Other measurements such as the Conicity index, the Waist-to-Height ratio, Waist Circumference, percentage of body fat, Waist-to-Hip ratio, Bioelectrical Impedance Analysis derived percentage fat mass, skinfold thickness, skinfold-derived percentage fat mass and neck circumference have also been associated with asthma. There is not, however, enough evidence to conclude which one is better suited to correlate asthma and obesity. It is also suggested that there may be the need to use different indexes depending on the gender and age of the child but once again there is not enough evidence to state which indexes would be better in each situation. It is suggested that in children aged 2-5, the Conicity Index, waist/hip circumference, Waist-to-Height ratio, skinfold thickness, and skinfold-derived percentage fat mass would be the better measurements while in children aged 9-13 the Conicity Index, Waist Circumference, Waist-to-Height ratio, skinfold thickness, skinfold-derived percentage fat mass, Bioelectrical Impedance Analysis derived percentage fat mass and Body Mass Index would be the better options.

It is interesting to note that the U-shaped association of asthma with body mass asthma suggests that sub nutrition, an opposite of obesity, is also associated with a greater risk of asthma. However, this topic still needs further research.

If we accept that there is a connection between asthma and obesity, a better correlation between asthma and a certain index may be an indicator that that index is the most reliable measure of obesity, at least in the paediatric population. Nonetheless, it is also important to take into account that other factors may be involved in this correlation, such as there being a different association between obesity and asthma depending on the pattern of fat distribution.

Important to note is the fact that most reviewed articles focused on the unilateral relationship between obesity and later asthma, i.e., obesity increases the risk for asthma. The few articles that studied the relationship in both directions suggest that asthma is associated with an increase in the Body Mass Index albeit only happening in new onsets of the disease. This increase is believed not to be due to a diminution of physical activity. Asthma increasing the Body Mass Index is further evidence supporting the link between these two diseases as it reinforces the idea of a common pathogenic pathway in both asthma and obesity and that there may be a genetic component.

Even though the aetiology of this relationship is not known yet, the underlying process seems to be a systemic inflammation. Serum leptin is also higher and adiponectin lower in these patients. Vitamin D deficiency also seems to play an important role in obese asthmatic albeit not clear what it does, yet. These underlying processes may be of the utmost importance not only for leading to a better understanding of the obese-asthmatic pattern but also to identify if there are increased risks of other diseases in these patients.

The asthma-obesity phenotype is also associated with a worse asthma control; therefore, weight loss may reduce the severity of the symptoms and the need of rescue medication. These children are also more likely to need to visit the emergency department than their overweight or lean counterparts, which is not surprising considering that their control is worse. In line with this information is the fact that if they require being admitted into hospital, they still have a worse prognosis - higher risk of requiring mechanical ventilation, higher mean total hospital charges, and longer mean length of hospital. There is, however, a number of articles stating that either there is no increase in asthma severity/control or that this association is only found in certain groups.

Lung function alterations described above may be partially responsible for this severity increase in the asthmatic-obese phenotype.

Gastro-oesophageal symptoms are of the utmost importance in the discussion of the correlation between asthma and obesity since they are crucial to the discussion of misdiagnosed asthma in obese children. Gastro-oesophageal symptoms may mimic asthma symptoms and, therefore, may induce a wrong diagnosis. This is further supported by the fact that asthmatic-obese children with gastro-oesophageal symptoms have worse asthma symptoms but have better lung function. It is also a possible explanation to why obese asthmatic patients have a worse control of their asthmatic symptoms – it may be a misdiagnosis hence the wrong disease is being treated. This would also be compatible with improvement of the symptoms upon losing weight.

Conclusion

Asthma and obesity, two extremely prevalent diseases in children worldwide are very likely to be correlated even though the underlying mechanism remains unknown. Further research into the different obesity indexes is warranted since it is not possible yet to determine which one better correlates with the phenotype in question. The Body Mass Index-Z, despite its widespread use, has long been questioned as an obesity index and this research may help in determining better alternatives. It is important to note that weight over the ninetieth percentile for their age and the Body Mass Index-Z are the indexes that have more evidence in favor of a link with asthma amongst the reviewed articles.

Since most research is focused on the risk of asthma in obese children it is also needed to further study the obesity risk in asthmatic children. This knowledge may allow physicians to better understand the aetiology of obesity in the asthmatic-obese children and, therefore, help in determining the most efficient techniques to lose weight in this population. The reviewed data on this topic points towards a two-way relationship between asthma and obesity.

In terms of the aetiology of this process, most of the evidence seems to lead to a systemic inflammation that underlies the obese-asthmatic phenotype. Even though there is evidence pointing to different participating components, a broader understanding and a better integration of the available knowledge is still needed. This better understanding is also crucial for differentiating true cases of obesity and misdiagnosis, which in turn may help clarify whether there is an actual severity increase/worse asthma control in this phenotype or if these results are partly explained by a misdiagnosis.

Evidence also suggests that asthmatic-obese children have more symptoms and that those are more difficult to control. On the one hand, what this could mean is that a better understanding of this correlation would even be helpful for healthcare management as these children require more assistance and once admitted to hospital need more thorough care than their overweight or lean counterparts. Even if in the short term costs would go up from financing research, on the long term, a more efficient approach to the disease would help reduce costs than could be used towards other diseases. On the other hand, this could be due to a reported misdiagnosis amongst obese-asthmatic children and obese children with gastro-oesophageal reflux symptoms – this could explain the poorer response to medication since a wrong therapy was being employed.

As a conclusion, the relationship between asthma and obesity has been a much-researched topic in recent years, yet, there is still much to clarify. This will require a continuous effort from the scientific community to continue progressing so that better treatments and a better life could be given to all the children presenting this phenotype. The research should be focused both on the aetiology of this bidirectional association as well as on the specific complications and treatments that might arise.

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